2-6-78

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: February 3, 1978

SUBJECT: CHEVRON Naled Technical EPA Registration#239-1633
Caswell#586 (Naled)

FROM: William Dykstra, Ph.D 2/3/78 WJD
Toxicology Branch

E for WOB 2/6/78

TO: Franklin Gee (16)

Action Type: Submission of toxicology data and validation of data by CHEVRON

Product Manager: Franklin Gee (16)

Recommendation:

1. The certification of the I.B.T. teratology study by Lorin R. Stelzer of the Chevron Chemical Company has not been certified on EPA report forms.

2. The teratology study requires that additional information regarding the establishment of the maximum tolerated dose in this study be furnished to the reviewer for evaluation. Although 0.3 mg/kg/day was the highest dose level tested and was stated, according to a pilot study, to represent the maximum tolerated dose, it appears that this dose level is inordinately low in comparison to the LD_{50}. Detailed results, including the MTD criteria used, of the pilot study must be furnished for evaluation before the teratology study can be fully considered in assessment of human safety.

3. The validation report by Dr. F. Kamienski does not alter the evaluation of the teratology study.

Review

1. Teratogenic study with Naled technical in Albino Rabbits (Industrial Bio-Test Laboratories, Report No. 8580-08991, 8/24/77; submitted by CHEVRON 10/17/77)

Test Material: Naled Technical (90%)

The animals employed in the study were 51 New Zealand albino rabbits. The animals were divided into three groups; 1 control group (C) and 2 test groups (T-I and T-II). Astructural outline of the experiment is provided below:

(1)

Group	Test Material	Dose*	No. of Inseminated	Number of** pregnant does
Control	none	-	17	12
T-I	Naled Technical	0.1 mg/kg	17	10***
T-II	Naled Technical	0.3 mg/kg	17	10

*Dose levels were selected based on the results of a pilot study. T-II is the MTD.

**Does not include the pregnant animals that died during the investigation.

***Data from the pilot study for Doe 21 was used in the report in order to obtain enough information for the minimum member of pregnant animals needed at the T-I level (See Validation)gestation day 0 was the day of insemination. Each female received an intravenous injection containing 2.0 mg of pituitary lutenizing hormone per kg of body weight and was inseminated with 0.7 ml of diluted pool semen from proven bucks. Bred does were housed individually.

All does received the test material via gelation capsules (no. 0) from gestation day 6 through day 18 inclusive (a total of 13 doses). Control animals were treated with gestation days. The most recent body weight was used in dose calculation. All animals were allowed food and water ad libitum.

The body weight of each animal was determined at the start of the investigation (gestation day 0). The animals were then weighed on gestation day 6, 9, 12, 15, 18, and sacrifice.

The animals were observed daily for mortality and abnormal reactions. All females were sacrificed by cervical dislocation on the 29th day of gestation. An incision was made in the abdominal wall and the full extent of both uterine horns was exposed immediately. Fetal swellings and implantation sites were counted, special attention being paid to resorption sites or any other uterine abnormalities. The number of viable fetuses present in the uterus was determined. All fetuses were removed from the chorion after cutting the umbilical cord and then weighed. An external examination of the fetuses was conducted with special attention paid to detection of the following abnormalities: craniofacial defects (including cyclopia, cheiloschisis, anophthalmia, microphthalmia, prognathism, micrognathia, and externalear abnormalities in size, shape or position), unusal size or position of the limbs, number and disposition of the digits, anurous condition, umbilical hernia, gastro-schisis, spina bifida and scoliosis.

Immediately after external examination, the viable young were placed in an incubator at 37 °C. Observations for viability, as indicated by respiratory and paw movements, were made hourly for 7 hours and again after 24 hours.

All young were examined by dissection. Particular attention was paid to any differences in size, shape, and orientation of the major organs and blood vessels. An examination of skeletal tissue was then performed employing a method described by Hurley.

Results: Body weight data, obtained throughout gestation, indicate no change which could be attributed to treatment with Naled Technical.

Thirteen does (3 control, 4 T-I and 6 T-II) died during the investigation the apparent cause of death was respiratory insufficiency or failure. Gross pathologic examination of these animals revealed no findings which could correlate with treatment of Naled Technical. No abnormal reactions were noted for any of the animals during the investigation. No dose-or test material related effects could be attributed to treatment with regard to number of pregnant does, number of implantation sites, number of resorption sites (early and late), number of does showing resorption, number of live young, number of resorption sites per 100 implantation sites, number of live young per 100 implantation sites, number of fetuses aborted or number of does showing abortion.

The mean body weight of the progeny obtained from all groups were comparable.

Examination for fetal external abnormalities diclosed no dose or test material-related effects which could be attributed to prenatal exposure to Naled Technical.

Prenatal treatment with Naled Technical did not affect the 24 hour survival of the young.

Dissection of young from treated females revealed no gross internal abnormalities.

No skeletal abnormalities were noted among fetuses in any of the levels tested. Observation of fetal skeletal development disclosed no dose - or test material related effects which could be attributed to prenatal exposure to Naled Technical.

Conclusion: No teratogenic or embryo-toxic effects were observed at 0.3 mg/kg/day from gestation day 6 through 18 inclusive. This teratology requires that additional information regarding the establishment of the maximum tolerated dose (MTD) in this study be furnished for evaluation. Although 0.3 mg/kg/day was the highest dose level tested and was stated, according to a pilot study, to represent the maximum tolerated dose, it appears that this dose level is inordinately low in comparison to the LD_{50}. Detailed results, including the MTD critieria used, of the pilot study must be furnished for evaluation before the teratology study can be fully considered in assessment of human safety.

Classification: Not acceptable in present form until additional information requested above is furnished.

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2. Validation of teratology Report by CHEVRON

Name of Validator: Francis Kamienski, Regulatory specialist from CHEVRON.

Curriculum vitae: Included

Exhibit B:

Clarification of Procedures

1. The number of pregnant animals.

The final report states: "Data from the pilot study for Doe 21 was used in the report in order to obtain enough information for the minimum number of pregnant animals at the T-I level.

Explanation: The total of pregnant T-I does was 9 rather than 10 during the main study. Summary Tables II, III, IV, V, VI, VII, VIII, IX, and individual animal data Tables XI, XIV, XVII, XXII have been recalculated and reflect values deleting the data from animal-No. 21. The recalculated tables are presented as Exhibit C.

Conclusion: The data recalculated and presented in the above Tables does not change the no effect level or conclusions made in the teratology study. The study is still regarded as potential core-minimum data after validation, subsequent to information requested on pilot study.

2. Breeding/Hormone injections

Comments: It cannot be verified from the raw data that each female received an intravenous injection of 2.0 mg of pituitary luternizing hormone per kg of body weight. The hormone injection was called for in the test XXXXXXXX protocol but there are no raw data records to show that it was actually administered.

3. Dosage and Feeding

Comment: It cannot be confirmed from raw data records that solvent control or Naled Technical were administered to test animals on day 6 through 18 of gestation. Also raw data records do not clearly indicate that specified dosage of solvent control and Naled Technical were administered on basis of most recent body weights.

The correct capsule size was confirmed as a No. 0 by Dr. Jenkins (IBT) in a September 27 telephone conversation with F.X. Kamienski.

4. Mortality/Reproductive Effects

Comments: There were a total of 12 pregnant does which died at various times during the study. These mortalities and corresponding reproductive parameters as recorded in th raw data are summarized.

There was no raw data concerning the condition of fetuses from the pregnant does which died during the study.

5. Statistical Analyses

Comment: The summary conclusions are believed to be valid although Statistical Analyses were not performed on any of the test data.

Conclusion: The validation report by Dr. F. Kamienski does not alter the evaluation of the teratology study.

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